65 yo M w/type 1 diabetes presents w/frequent hypoglycemia

Jess Hwang

4/4/13

HPI

- Diagnosed with diabetes at the age of 14
  - presented with symptoms of polydypsia
- No neuropathy, retinopathy or nephropathy
- On Orinase (SU) for 15 years, then insulin
- Started on an insulin pump 2002
- Exercises 3 times per week
- Diet is fairly healthy
- Nocturnal hypoglycemia 3 times per week

PMH

- Dyslipidemia
- Diabetes
- Mildly elevated PSA

Social history

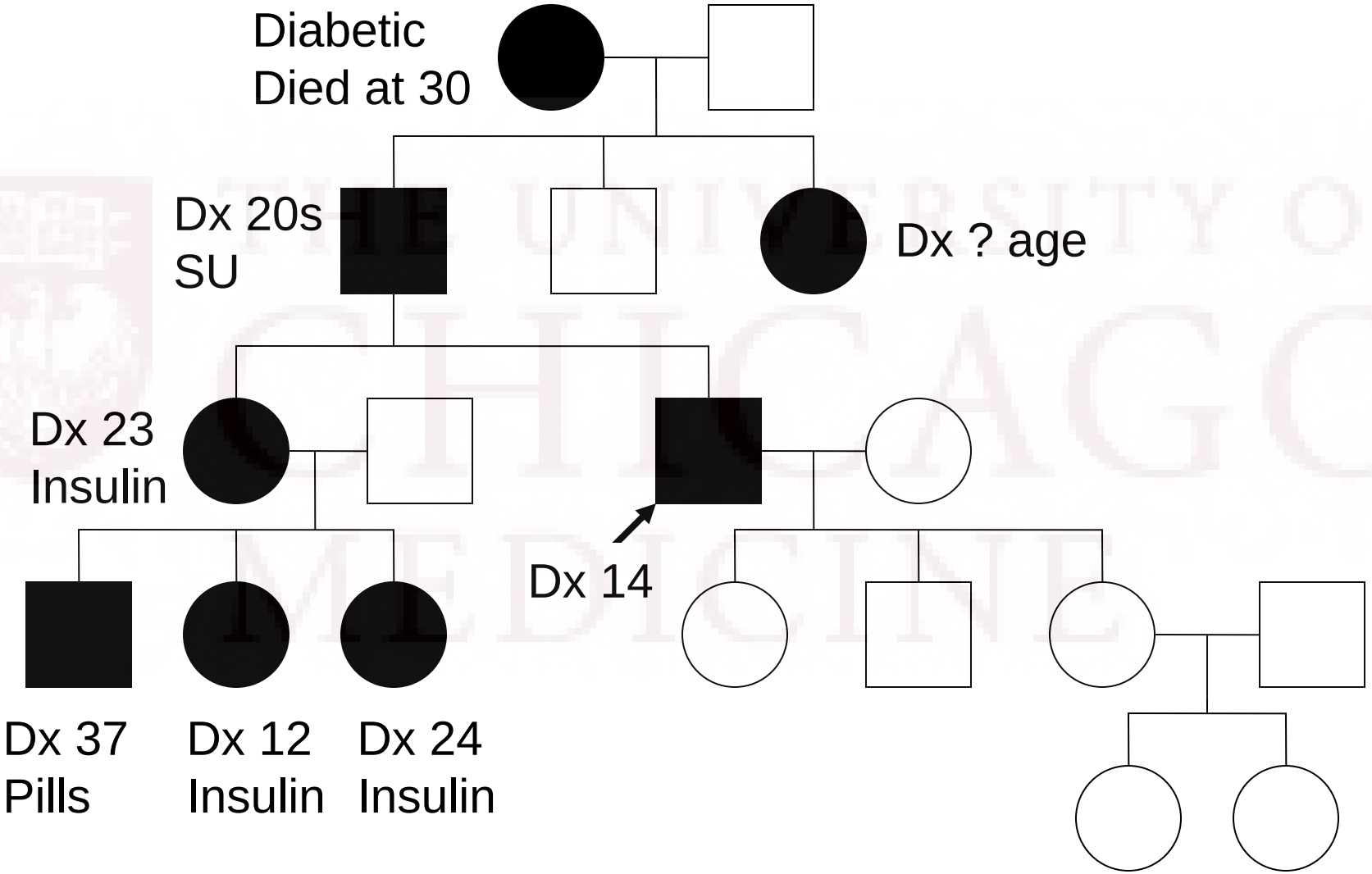
- Engineer/consultant
- Lives with wife
- No tobacco, EtOH

Family history: pending

Medications

- Lovastatin
- Ergocalciferol 1000
- Medtronic insulin pump
  - Basal (24h = 10.63U)
  - Carb ratio 10-11
  - ISF 40
  - Target 95-110

Pedigree



^^Per redcap survey data and medical chart

Physical exam

Vitals: 140/74 75 6’5” 188lb (85kg) BMI 23.5

HEENT: PERRLA, EOMI

Neck: no thyromegaly, no nodules

CV: RRR, no murmurs

Lung: CTA bilaterally

Abdomen: soft, nontender, non-obese

Skin: no acanthosis nigricans

Extremities: no edema, good pulses

Labs

141	102	20	122
3.9	30	1.0	8.8

6.9	4.3
0.7	75
23	26

C-peptide 0.12

HbA1c 6.5%

GAD65 neg

Lipid: HDL 65, LDL 80, TG 96

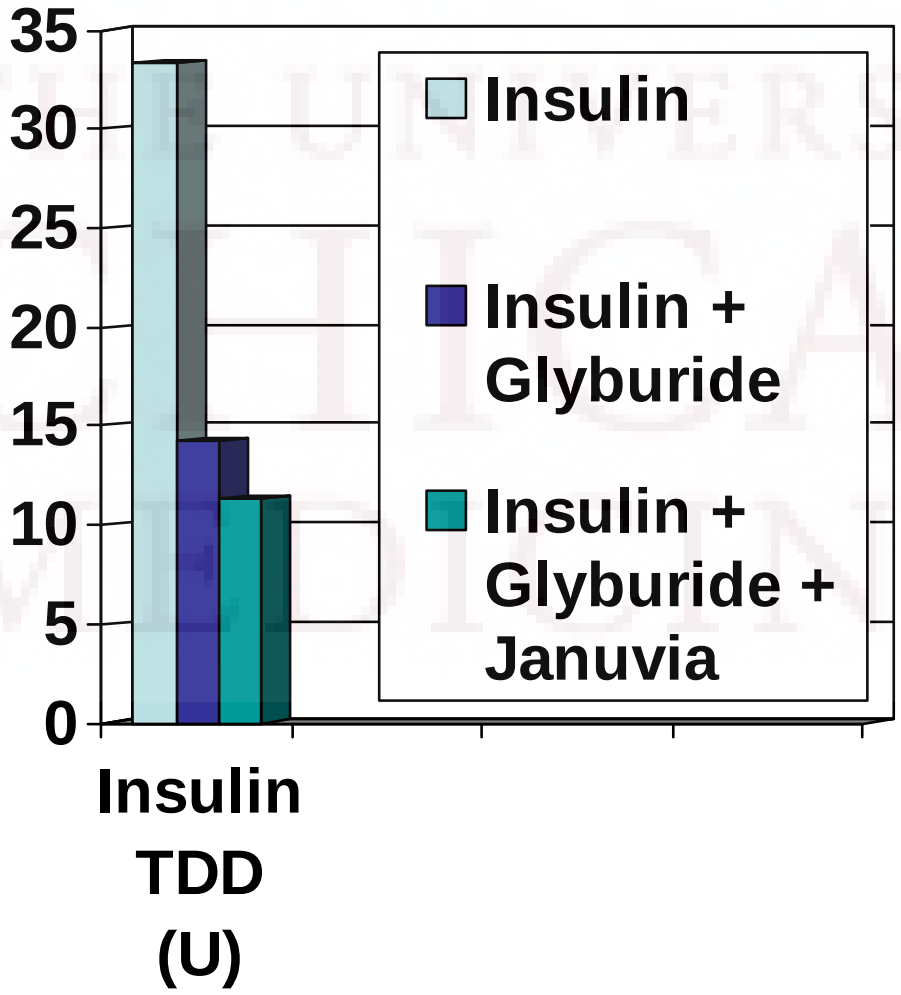
Genetic testing

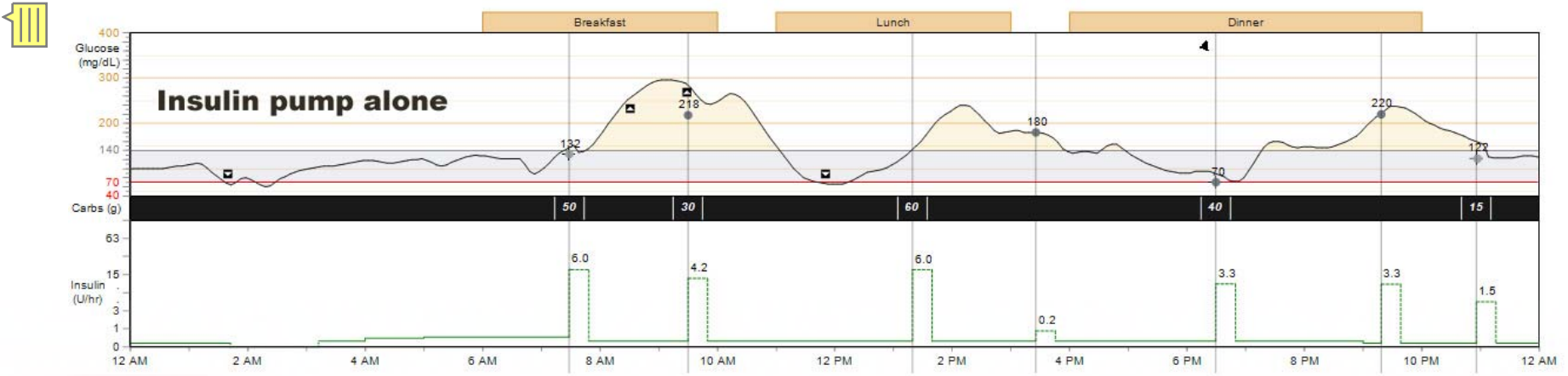
HNF1A: c.526C>CT, p.176Q>QX

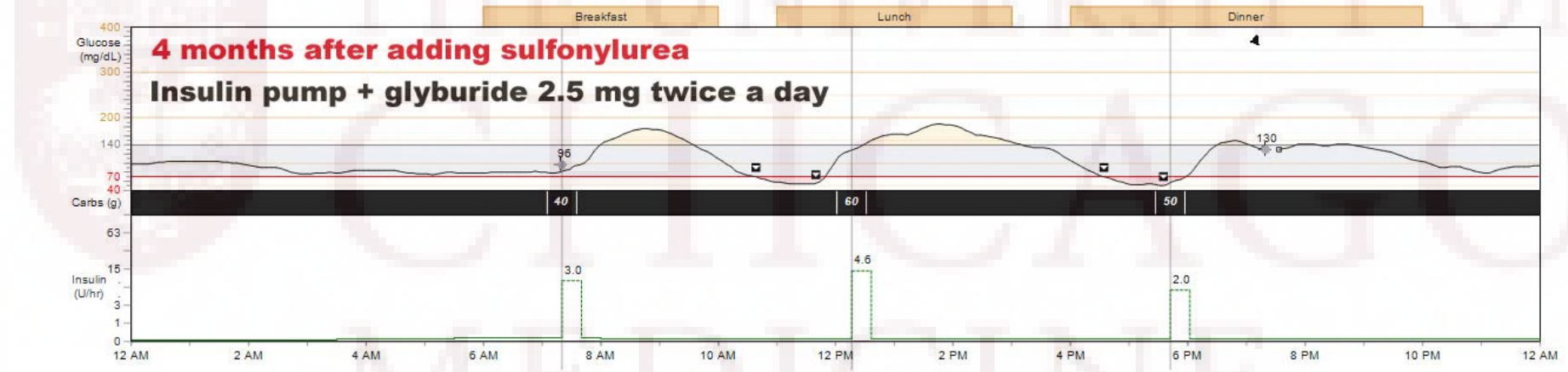
- Premature stop codon in exon 2 of *HNF1A*
- Previously reported nonsense mutation
- Associated with Maturity-onset Diabetes of the Young (MODY) Type 3

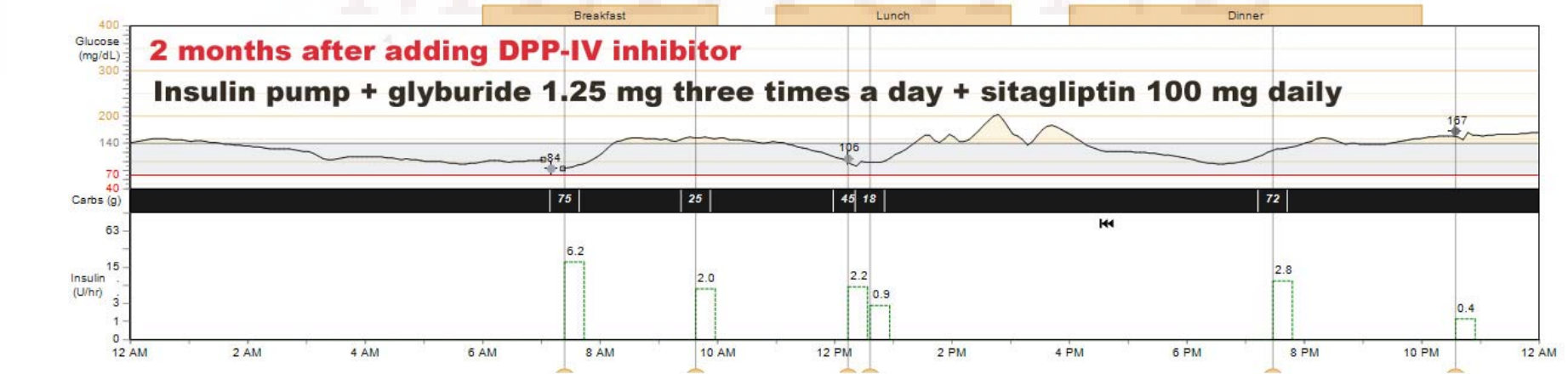
	Prior to transition	+6 months	+2 months
Therapy	**Insulin pump**	**Glyburide 2.5 BID Insulin pump**	**Glyburide 1.25 TID Januvia 100 mg Insulin pump**
Avg BG (mg/dL)	135 ± 46	135 ± 54	141 ± 58
Sensor BG (mg/dL)	128 ± 41	127 ± 43	125 ± 45
HbA1c (%)	6.1	6.1	6.0
Insulin TDD (U)	33.3 ± 5	14.3 ± 4.2	11.3 ± 2.9

Insulin Total Daily Dose




Breakfast
Lunch
Dinner
Glucose (mg/dL)
400
300
200
140
70
40
Insulin pump alone
132
218
180
70
220
122
Carbs (g)
50
30
60
40
15
Insulin (U/hr)
63
15
3
1
0
6.0
4.2
6.0
0.2
3.3
3.3
1.5
12 AM
2 AM
4 AM
6 AM
8 AM
10 AM
12 PM
2 PM
4 PM
6 PM
8 PM
10 PM
12 AM


Breakfast
Lunch
Dinner
Glucose (mg/dL)
400
300
200
140
70
40
4 months after adding sulfonylurea
Insulin pump + glyburide 2.5 mg twice a day
96
130
Carbs (g)
40
60
50
Insulin (U/hr)
63
15
3
1
0
3.0
4.6
2.0
12 AM
2 AM
4 AM
6 AM
8 AM
10 AM
12 PM
2 PM
4 PM
6 PM
8 PM
10 PM
12 AM


Breakfast
Lunch
Dinner
Glucose (mg/dL)
400
300
200
140
70
40
2 months after adding DPP-IV inhibitor
Insulin pump + glyburide 1.25 mg three times a day + sitagliptin 100 mg daily
84
106
167
Carbs (g)
75
25
45
18
72
Insulin (U/hr)
63
15
3
1
0
6.2
2.0
2.2
0.9
2.8
0.4
12 AM
2 AM
4 AM
6 AM
8 AM
10 AM
12 PM
2 PM
4 PM
6 PM
8 PM
10 PM
12 AM

Clinical Questions

- When to consider testing for MODY?
- Pathophysiology of *HNF1A*-MODY?
- Pharmacotherapy in *HNF1A*-MODY?
  - Efficacy vs Metformin
  - Hyperexcitability to SUs
- Incretin-based therapy as alternative or adjunct to SU?

Criteria for considering testing

- Diabetes in 2+ generations (AD pattern)
- Diagnosis < 25 years of age

- Non-obese
- Non-insulin dependent (or on low doses)
- Type 1 like- with negative antibodies, detectable c-peptide years after diagnosis

Naylor R, Philipson LH. Clin Endo 2011;75:422-426.
Fajans SS, Bell GI. Diab Care 2011;34:1878-1883

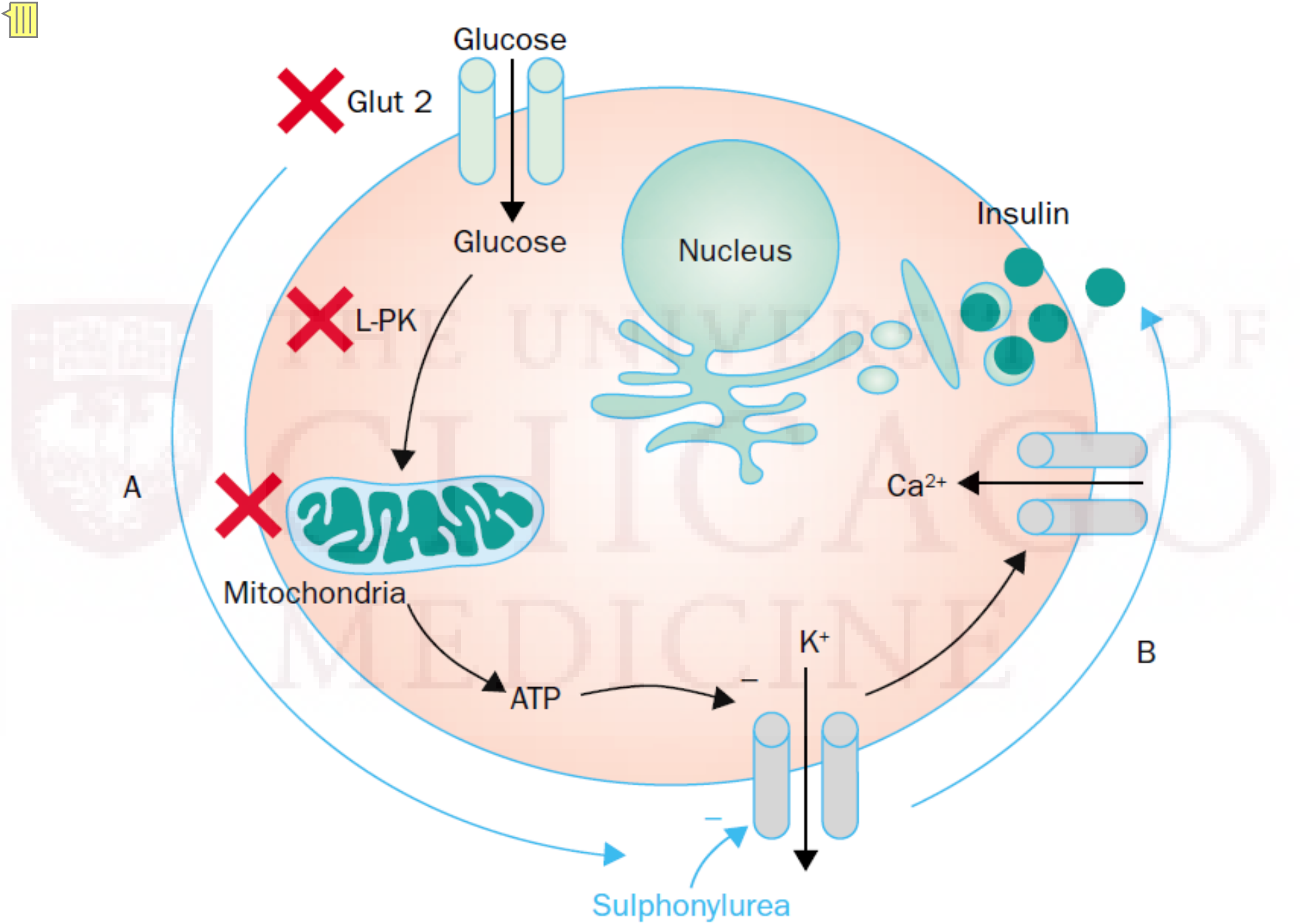
HNF1A-MODY

- Most common cause of MODY in the UK
- Autosomal dominant inheritance
- Highly penetrant
- At risk for micro/macrovascular complications
- ?Phenotype:
  - Low renal threshold for glucose
  - Decreased hsCRP

Pathophysiology of *HNF1A*-MODY

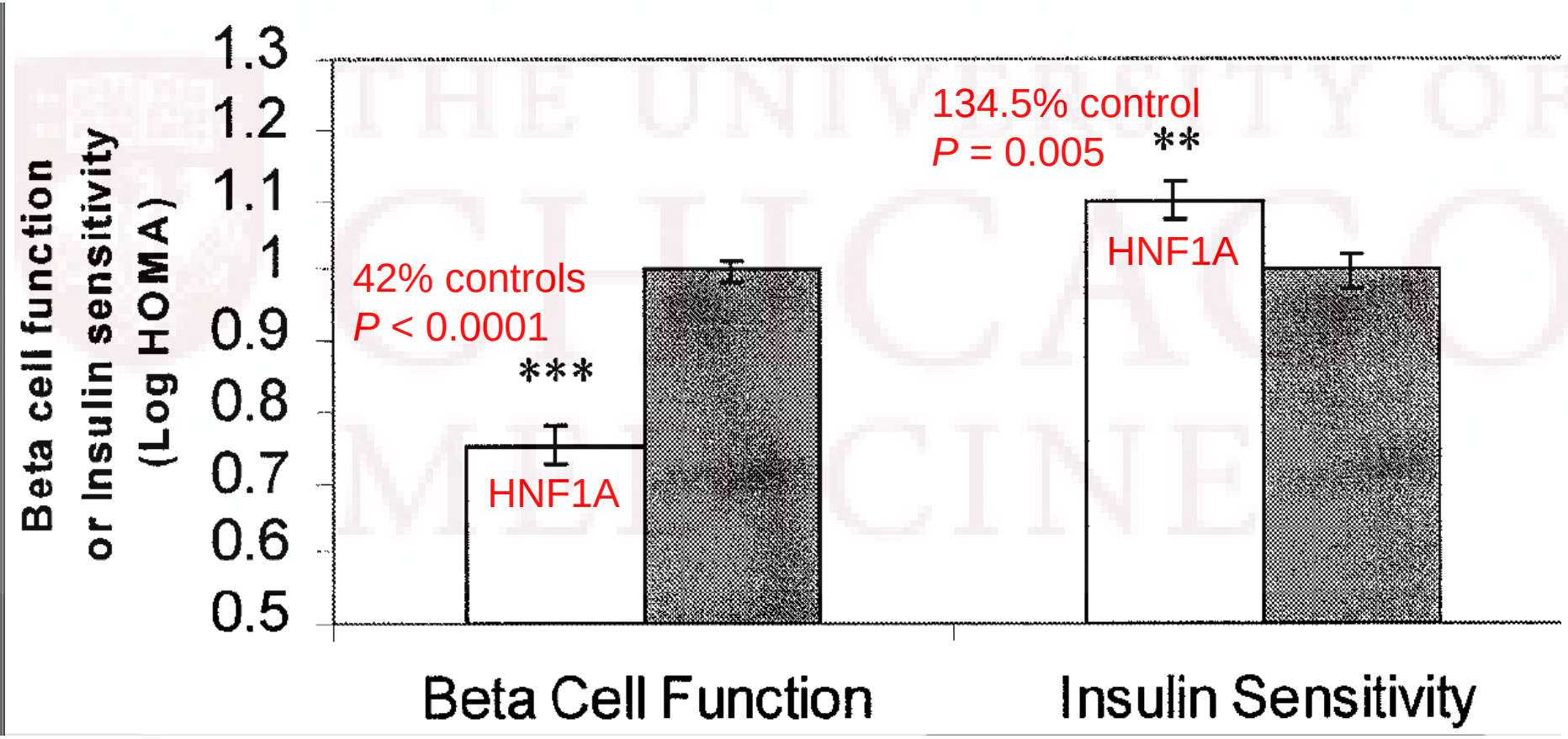
- Progressive beta cell dysfunction
- Reduced insulin secretion to glucose
- ?Beta cell apoptosis

- *HNF1a* -/- mice had decreased mRNA levels of proteins involved in glucose uptake and glycolysis (GLUT2, L-pyruvate kinase)



Pearson ER et al. Lancet 2003;362:1275-1281.

Pathophysiology of HNF1A-MODY

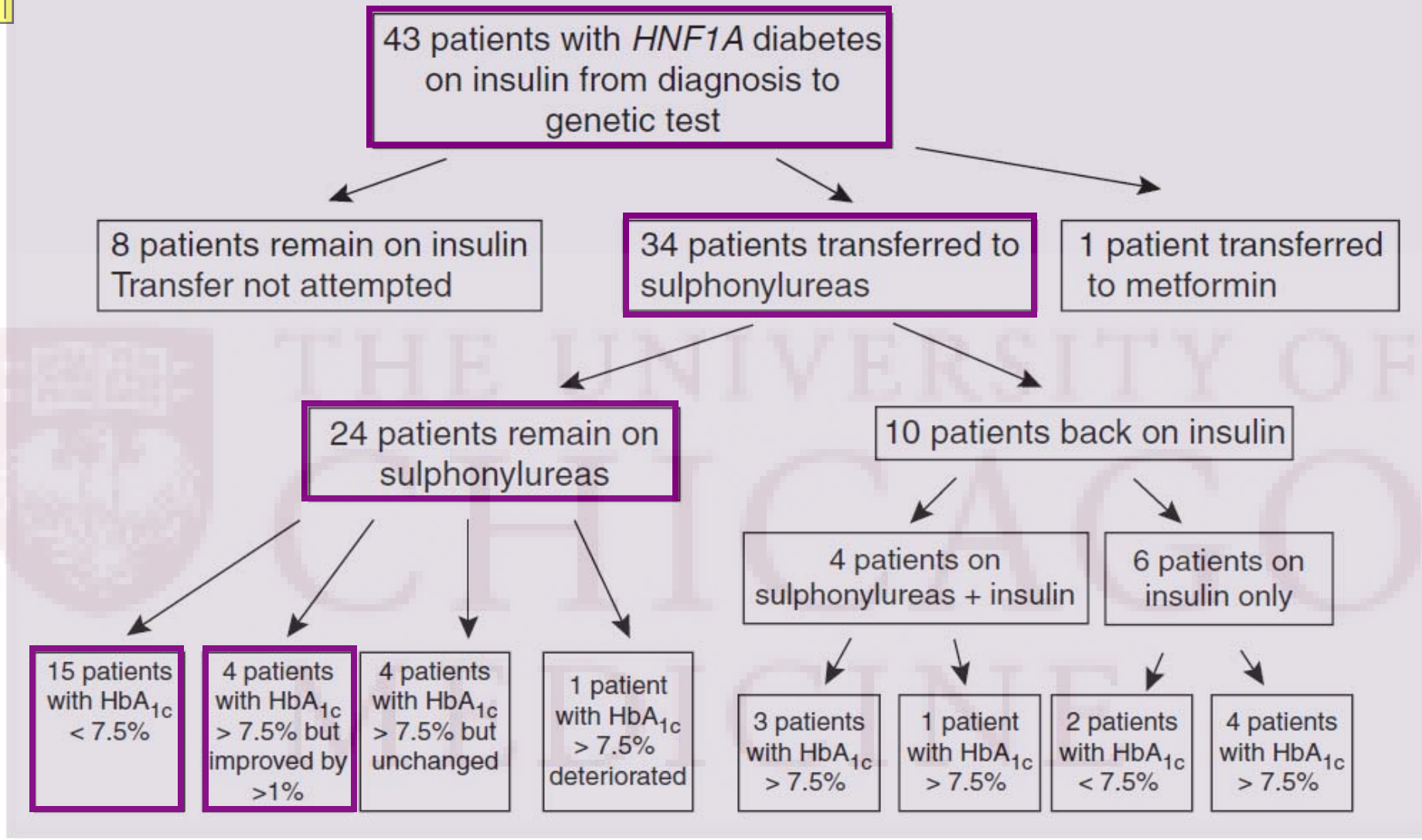


Pearson ER, et al. Diabetes 2001;50(1):S101-S107.

Clinical implications

- Observational study
- Aim: Investigate clinical course of patients transitioning from insulin→SU after *HNF1A* diabetes is confirmed.
- N = 43 patients
- Success: HbA1c < 7.5% or improvement of pre-transition HbA1c of >1%

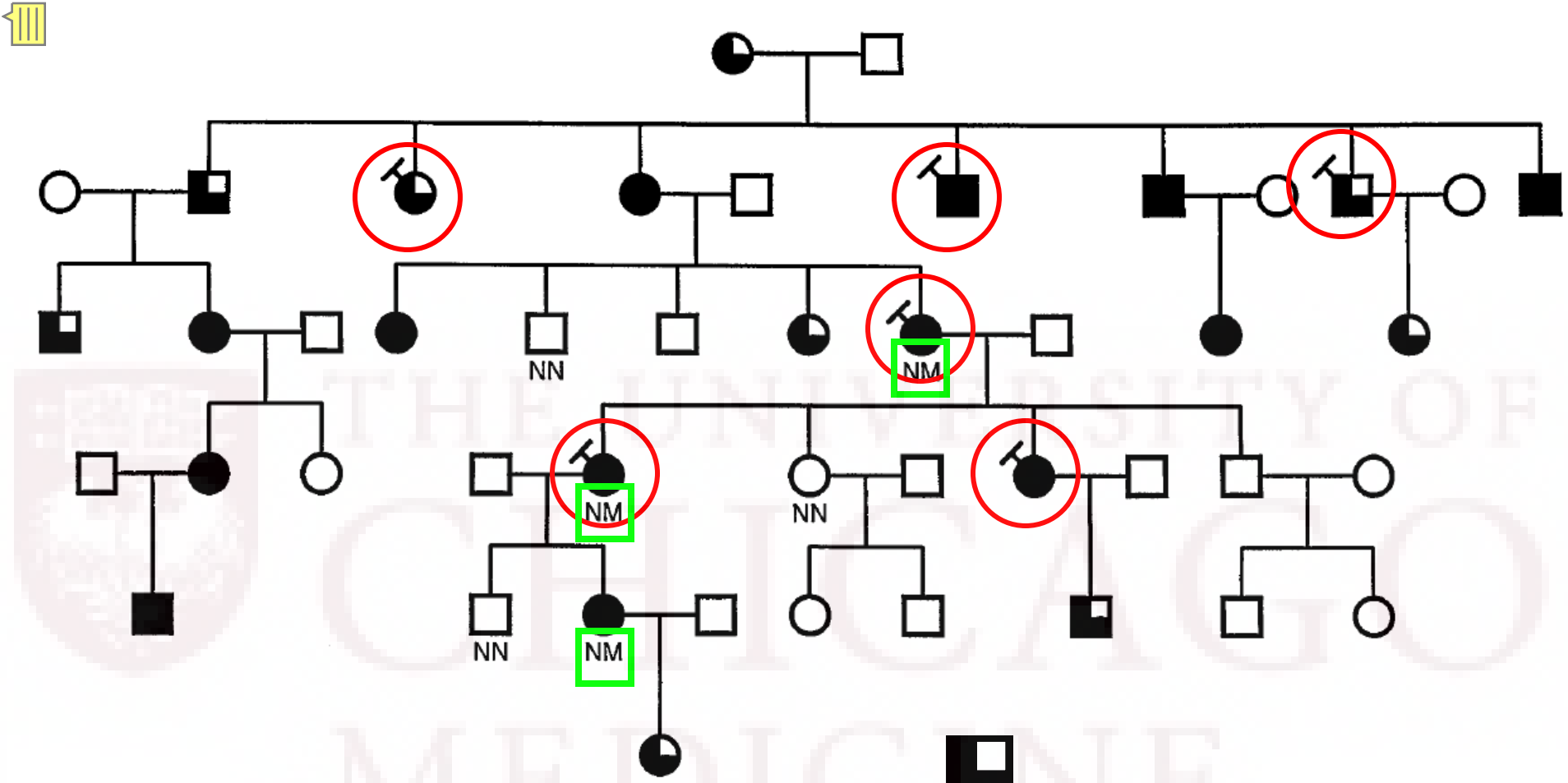
Shepherd M, et al. Diabetic Medicine 2009;26:437-441.



Finding HNF1A mutation does influence physicians' treatment decision

Transferring from insulin to SUs is successful in a majority of patients

Shepherd M, et al. Diabetic Medicine 2009;26:437-441.



Sulfonylurea Hyperexcitability

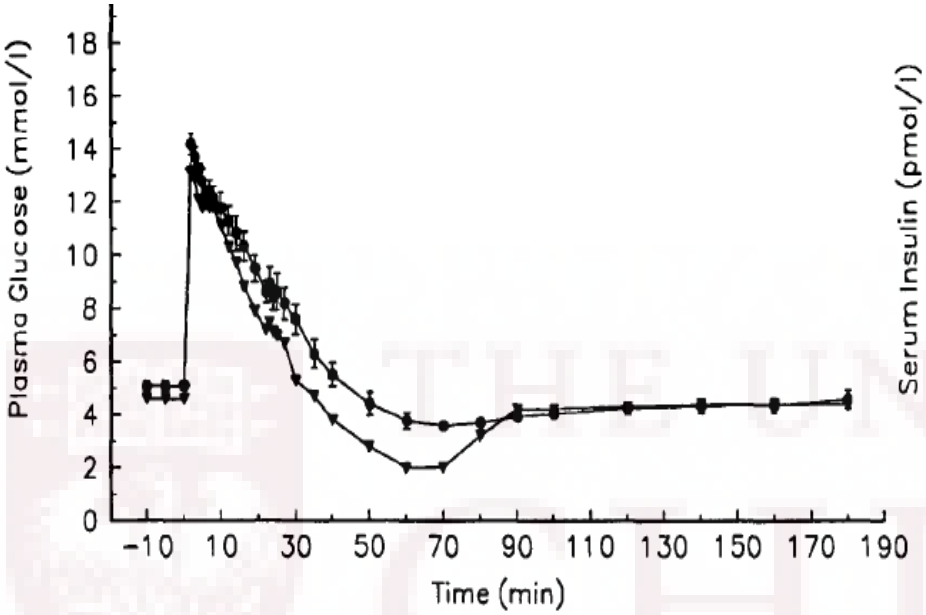
Suspected diabetic or IGT

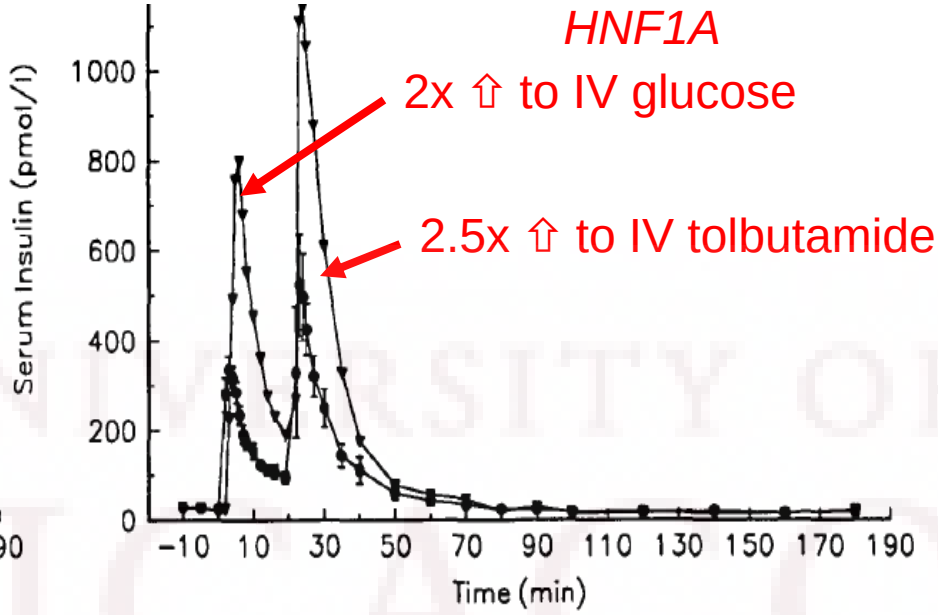
Hypoglycemia with SU

M *HNF1A* diagnosis

Sovik O et al. Diabetologia 1998;41(5):607.

Tolbutamide-modified IVGTT



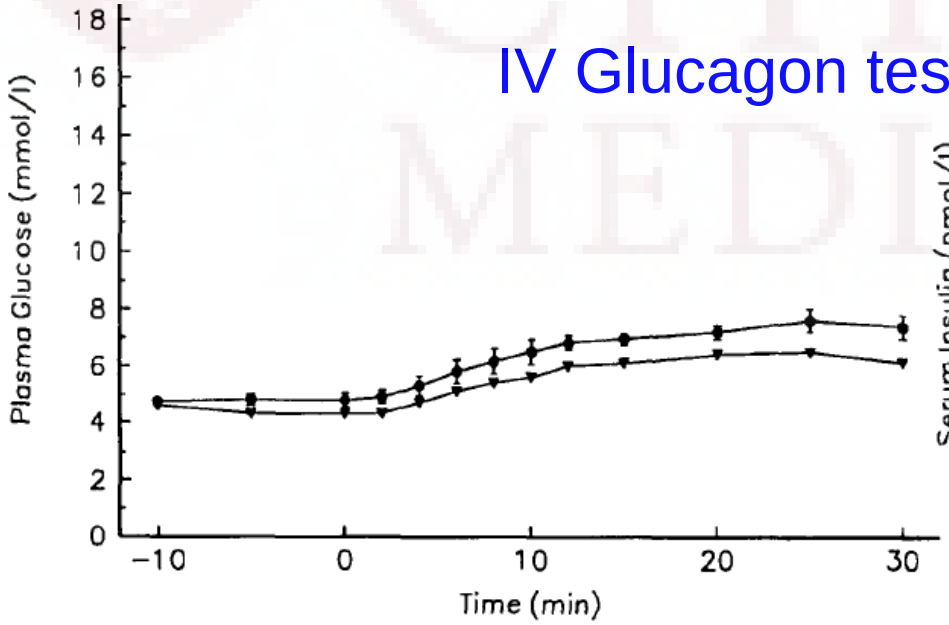


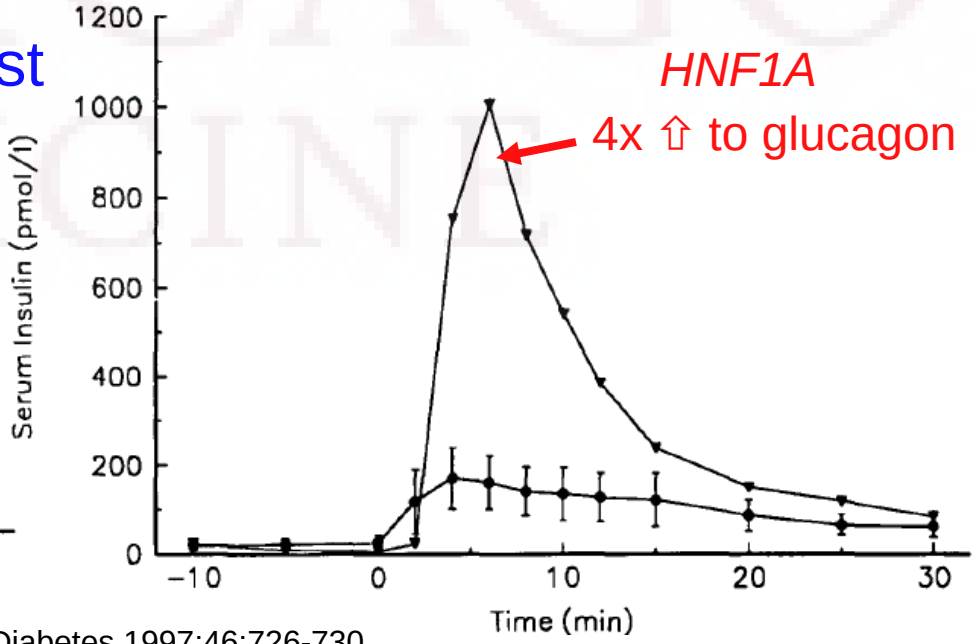
HNF1A

2x ⇧ to IV glucose

2.5x ⇧ to IV tolbutamide

IV Glucagon test





HNF1A

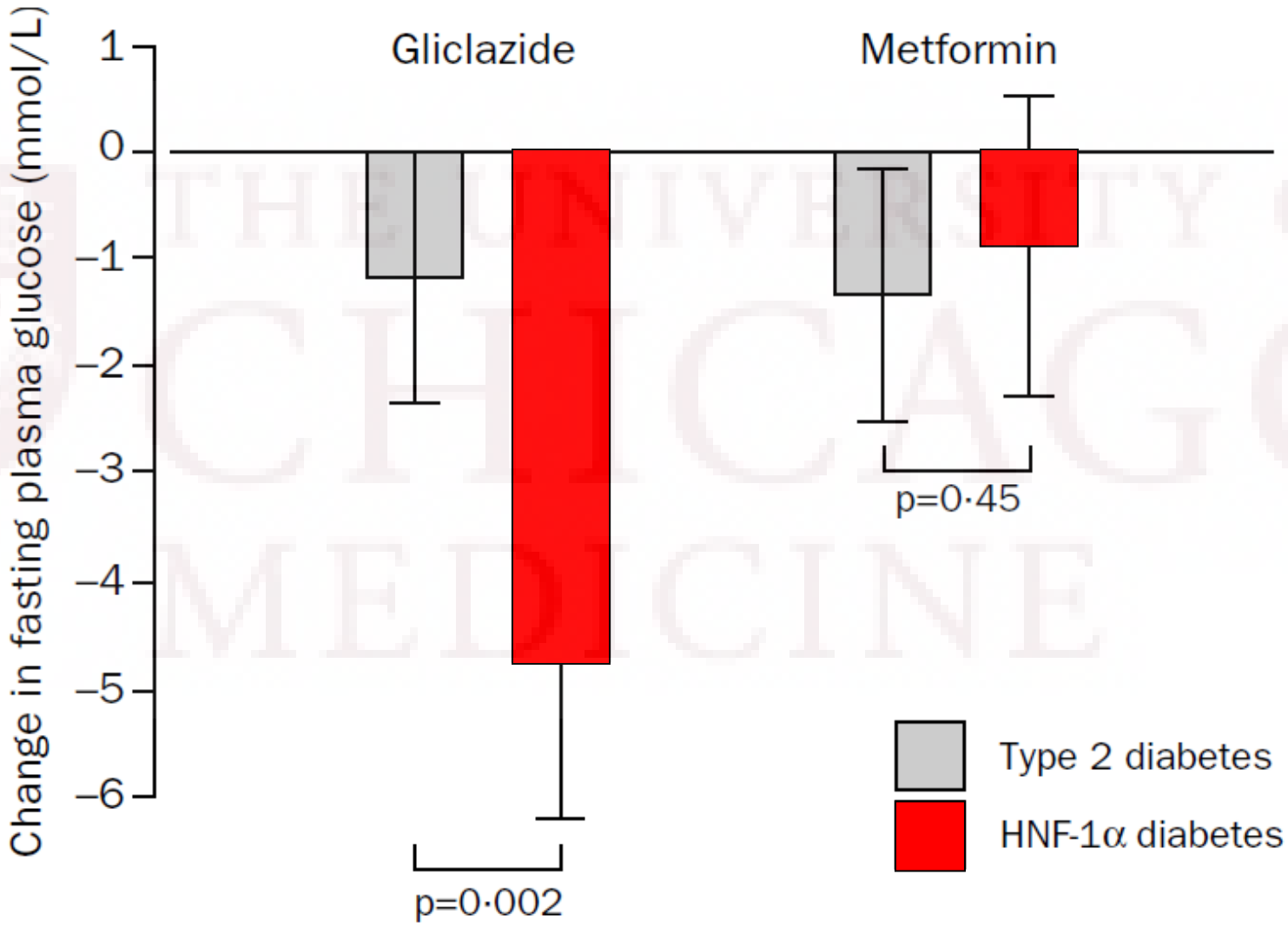
4x ⇧ to glucagon

Hansen T et al. Diabetes 1997;46:726-730.

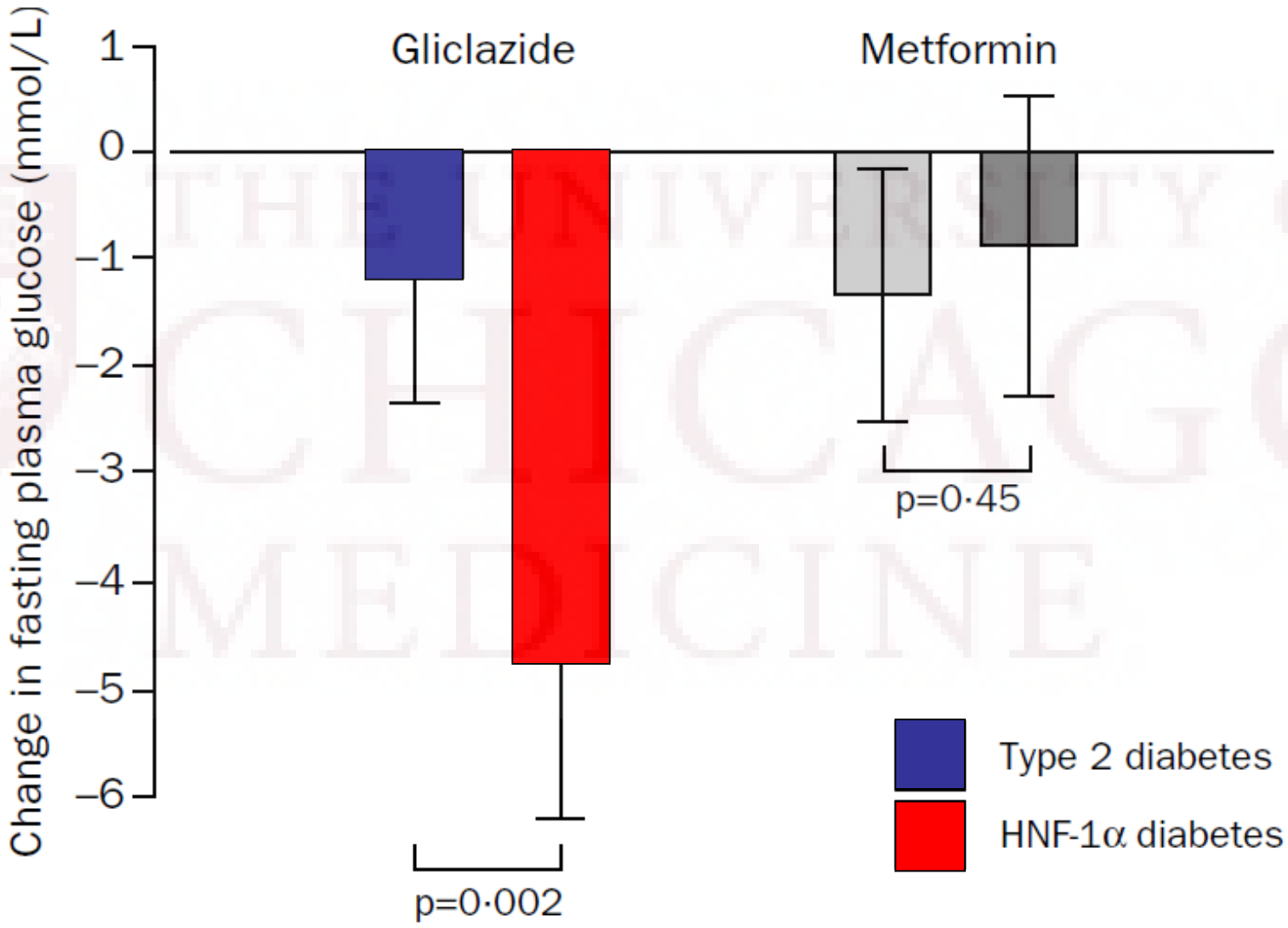
Metformin vs SU in *HNF1A*-MODY

- Randomized crossover trial (1 week washout)
- N = 36 patients
- Primary outcome = response of fasting plasma glucose
- Secondary outcomes = fructosamine, episodes of hypoglycemia

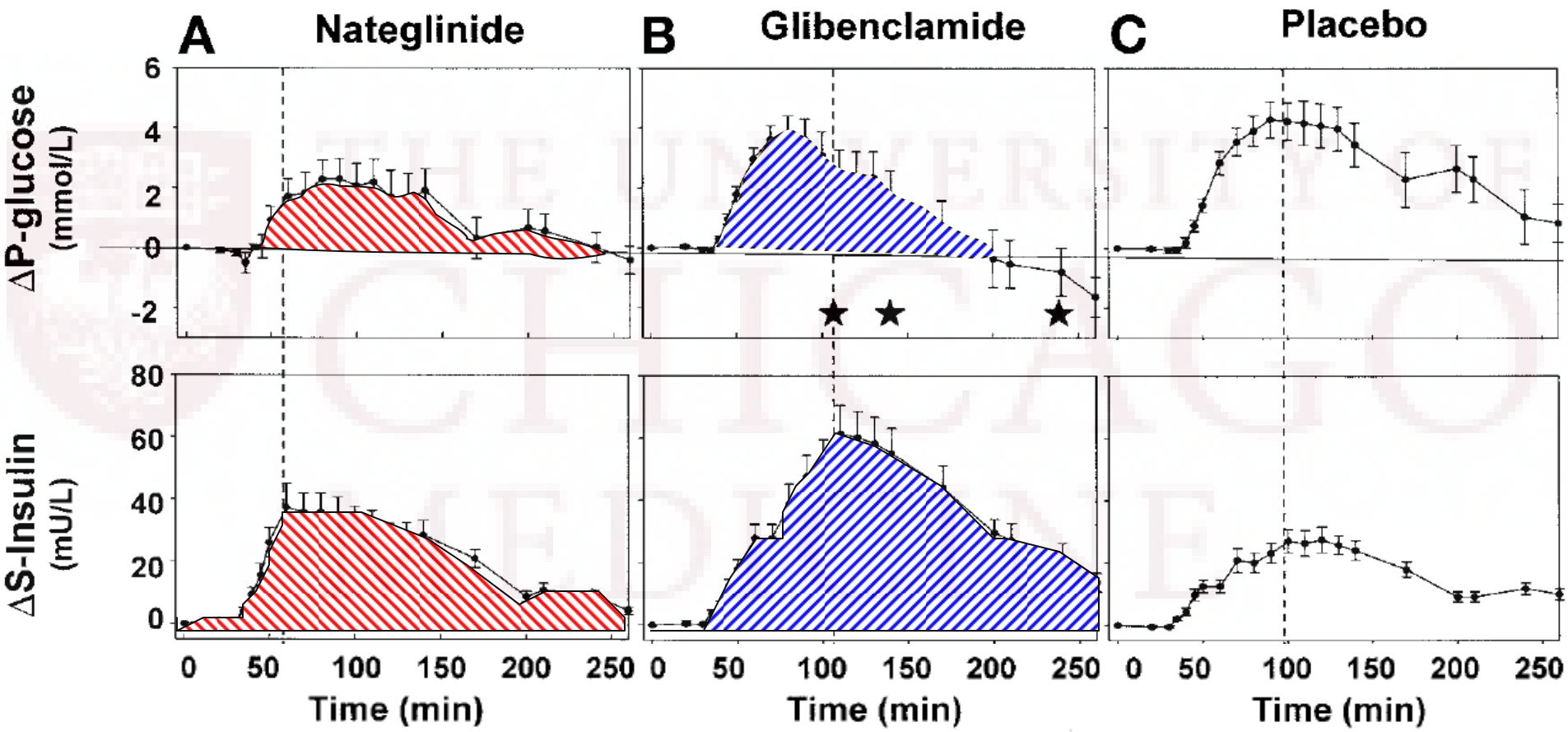
Metformin vs SU in HNF1A-MODY



Metformin vs SU in HNF1A-MODY



SU (Nateglinide) vs SU Glibenclamide



Low dose of nateglinide prevents acute postprandial rise in glucose more efficiently and causes less hypoglycemia than glibenclamide

Tuomi T et al. Diab Care 2006;29:189-194.

Incretin-based therapy in MODY

- Not well-defined… yet
- In the last 3 years, isolated case reports
- Ideal treatment would directly address the primary defect of declining beta cell function
- GLP-1 RA/DPP-4 inhibitors have a number of protective effects on beta cells including a reduction in apoptosis and beta cell preservation

Take Home Points

- Criteria for considering genetic testing
- Mechanism for the increased glycemic response to SUs seen in *HNF1A*-MODY
  - increased insulin secretory responses to SUs
  - increased insulin sensitivity
- Rapid onset, short-acting SUs (glinides) are good alternatives to long-acting SUs
- Incretin-based therapy needs to explored

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SAVE THE DATE

2013 Monogenic Diabetes Forum

July 17-20, 2013

Chicago, IL

We are excited to announce our second conference for families & individuals with monogenic diabetes.

Please join us for this interactive & educational opportunity to connect with others whose lives have been affected by genetic forms of diabetes.

More details to be announced in January 2013.